Predictive Value of Early Postoperative Course of Serum Cortisol After Transsphenoidal Surgery for Cushing's Disease

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Key words
predictive value, serum cortisol, transsphenoidal surgery, TSS, Cushing's disease, remission, predicting recurrence

received 19.03.2022
revised 04.07.2022
accepted 15.07.2022
published online 09.09.2022

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: 704–713
DOI 10.1055/a-1909-1639
ISSN 0947-7349

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ABSTRACT

Objective To identify early available predictors for the long-term outcome of patients after transsphenoidal surgery (TSS) in the management of Cushing's disease.

Methods This single-center, retrospective study included 93 consecutive patients with Cushing's disease (follow-up 12–129 months, mean 48, median 38) who underwent TSS (21 had previous operations elsewhere). Six cases had early re-operation, and the resulting data were evaluated instead of the respective first operation. During the postoperative course, serum cortisol levels were assessed every four hours at least until the next morning. An association of parameters with long-term outcomes was tested using binary logistic regression. Receiver operating characteristic curves were used to determine sensitivity, specificity, positive predictive value, and negative predictive value of different cut-off values of serum cortisol in the postoperative course in the event of recurrence after remission.

Results Eighty out of 93 patients (86 %) showed postoperative remission (after primary treatment, 60 out of 72 patients, 90.3 %). Of these, 8 patients (10 %) developed recurrence of hypercortisolism. Compared to patients with persisting long-term remission, those with recurrence differed in cortisol levels starting from 4 pm on the day of surgery plus an event of increasing cortisol during the early postoperative course ("peak"). Binary logistic regression showed the association between a peak of serum cortisol in the early postoperative course with an increased probability of recurrence.

Conclusions Patients with a peak of serum cortisol in the early postoperative course show an increased recurrence rate. A cut-off value of serum cortisol for clear identification of patients with later recurrence could not be determined.

Introduction

Cushing's disease is caused by prolonged exposure to supraphysiological high levels of cortisol due to an ACTH-producing pituitary adenoma [1, 2]. Typical symptoms include: obesity, full moon face with plethora, a diabetic metabolic condition, hypertension, amenorrhea, loss of libido and virility, osteoporosis, striae rubrae, and psychological changes. Patients with Cushing's disease have an increased risk of mortality in comparison to the healthy population [3–6]. Thus, the aim of this study was to identify possible early predictors of long-term outcomes of patients after transsphenoidal surgery (TSS) in the management of Cushing's disease. Patients at an increased risk of recurrence may particularly benefit from a more intensive post-op follow-up. In addition to predictive factors for the short- and long-term course of patients after TSS for Cushing's disease already described in the literature [7–9], the individual course of serum cortisol during the day of surgery, in particular, was examined more closely in this study.

Materials and Methods

This retrospective, single-center study investigated 93 patients with the endocrinologically proven diagnosis of Cushing's disease who underwent TSS at the Department of Neurosurgery, Johannes Wesling Klinikum (JWK) Minden, University Hospital of the Ruhr-University Bochum, from October 2007 to April 2019 (mean follow-up 48 months, range 12–129). All operations were performed under the supervision of the same surgeon (UJK).

The original patient cohort included 96 patients, on whom a total of 121 operations were performed. Exclusion criteria included a follow-up of < 12 months and a condition after bilateral adrenalectomy or hypophysectomy. Since the main difference between primary and late re-operations from a surgical perspective is the formation of scar tissue, early re-operation in which scar tissue formation is not advanced was counted as the respectively first operation, as proposed by Lüdecke et al. [10]. In this study, an early re-operation was performed on six patients (four patients with inadequate postoperative cortisol decline and two patients with early recurrence), who were verified by a low dose dexamethasone suppression test. In these six cases, the early re-operation and the associated data were evaluated instead of the respective first operation. In cases with incomplete data (follow-up < 12 months), informed consent was obtained from the patients to complete the follow-up with findings from the referring endocrinologist. Thus, a total of 93 operations on 93 patients were investigated.

In 21 of the 93 patients (22.6 %), TSS was performed as a (late) re-operation. In 72 patients (77.4 %), primary treatment (primary surgery or early re-operation within four weeks after primary surgery) was performed at JWK. All patients underwent a thin-slice MRI of the sellar region to localize the adenoma. Sinus petrosal catheterization was performed in patients with mismatching CRH stimulation and dexamethasone suppression tests and with negative sella MRI. Patients then underwent direct transnasal-transsphenoidal surgery using microsurgical technique and ultrasound assistance, as published previously [10, 11]. Serum cortisol levels were assessed twice intraoperatively and then every four hours until at least 8 am at POM1 (first postoperative morning). Plasma ACTH was also determined at POM1. Perioperatively, no glucocorticoids were administered unless secondary adrenal insufficiency was diagnosed by subnormal serum cortisol levels. Only then was hydrocortisone treatment initiated, starting with 150 mg per day, which was tapered to 40 mg per day on the day of discharge. Postoperative normal or elevated serum cortisol levels were considered indicative of residual adenoma.

Remission after TSS was diagnosed by subnormal cortisol levels (< 62 µg/L: lower end of the reference range for morning cortisol in the laboratory) and low dose dexamethasone suppression tests in cases of delayed cortisol decrease. The early postoperative outcome was divided into three categories: decrease in serum cortisol to the subnormal range (< 62 µg/L) within 24 h after the end of surgery (POM1 = early decrease), decrease in serum cortisol to the subnormal range after more than 24 h after the end of surgery (delayed decrease), and persistence of serum cortisol in the morning reference range (62–194 µg/L) or above (> 194 µg/L).

Any secondary increase of serum cortisol after an initial decrease during the day of surgery was defined as a "peak," independent of its height. The initial rise in serum cortisol levels immediately after surgery (usually within four hours) was considered a response to mechanical manipulation during surgery (▶ **Fig. 1**) and not taken as a peak.

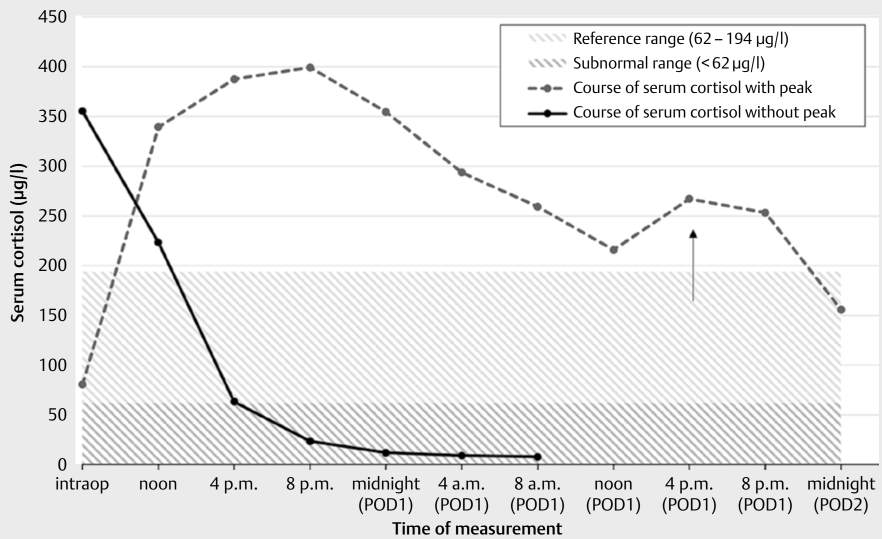
In case subsequent recurrence was suspected, patients underwent extensive testing by the referring endocrinologists, including detection of morning serum cortisol and plasma ACTH, dexamethasone suppression tests, CRH stimulation test, detection of midnight cortisol level and/or diurnal profile of cortisol. Long-term remission is defined as the persistence of adrenal insufficiency requiring hydrocortisone substitution or normalization of serum cortisol with a normal diurnal profile.

IBM SPSS Statistics 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, version 26.0. Armonk, NY) was used for statistical analysis. Shapiro-Wilk test was used in testing for normal distribution. Statistical tests for nominally scaled data included the χ^2-test or Fisher's exact test; for metrically scaled data, the unpaired t-test, ANOVA, Mann-Whitney U test, or Kruskal-Wallis test were used. An association between parameters and long-term outcome (recurrence yes/no) was tested by binary logistic regression. Receiver operating characteristic (ROC) curves were used to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different cut-off values of serum cortisol for the outcome of "long-term remission" vs. "recurrence" at different times of measurement. Optimal cut-off values were calculated using the Youden index.

Sensitivity in this context represents the percentage of patients with later recurrence after remission who had a cortisol value above a respective cut-off value (true positive rate). The PPV was the percentage of patients who had a cortisol value measured above this cut-off value and relapsed later. Specificity measured the proportion of patients with long-term remission who had a cortisol value below this cut-off value (true-negative rate). NPV was the proportion of patients in whom a cortisol value below this cut-off value correctly predicted long-term remission. The Youden index was used to determine the cut-off value at which the sum of sensitivity and specificity reached its maximum expression. At each measuring time, the sensitivities and specificities determined for the different cut-off values were plotted on a curve (▶ **Fig. 2**). The area under the curve (AUC) indicated the quality of cortisol levels for predicting recurrence.

In all calculations, results were considered statistically significant at a significance level of $p < 0.05$.

The study was approved by the ethics committee of the Ruhr-University Bochum, branch office Bad Oeynhausen, AZ:2018–357.



▶ **Fig. 1** Representation of a course of serum cortisol with (arrow) and without peak (intraop: intraoperative, POD1: postoperative day 1).

Results

A total of 93 patients were included in the study and underwent TSS for Cushing's disease. The female-to-male ratio was 3:1. The mean age at surgery was 42 years (range 13–71 years).

Out of 93 operations, an early cortisol decrease was achieved in 72 cases (77.4 %), and a delayed cortisol decrease was achieved in eight cases (8.6 %) (▶ **Fig. 3**). Thus, a total of 80 patients (86.0 %) showed postoperative remission. In 13 cases (14 %), no sufficient cortisol decrease to subnormal levels occurred.

Of the 80 patients with remission, eight patients (10 %) relapsed later on (after 2, 3, 10, 14, 16, 17, 21, and 48 months, respectively) and 72 (90 %) remained in remission. Compared to an early decrease of cortisol, the recurrence rate after delayed decrease was higher (37.5 % with delayed decrease vs. 6.9 % with early decrease, p = 0,03). Also, three of eight patients (37.5 %) with delayed decrease underwent re-operation, whereas only 12 of 72 patients (16,7 %) did so (p = 0,035). The long-term remission rate after operation at the JWK (including (late) re-operations after previous surgery elsewhere and primary surgery or early re-operations) was 77.4 % (72 of 93 patients). For patients without previous operations elsewhere, the remission rate was 90.3 % (65 out of 72). Of these, in seven cases (out of 65; 10.8 %), recurrence occurred, resulting in a long-term remission rate of 80.6 % (58 out of 72). Three of the six patients described above with the early re-operation showed long-term remission.

Comparison of cortisol levels regarding long-term outcome

Serum cortisol levels from 4 pm on the day of surgery to 8 am on POM1 of patients with long-term remission were statistically significantly (p = 0.001–0.016) lower than those of the patients with later recurrence after remission (▶ **Figs. 4,5**; ▶ **Table 1**). However, no clear cut-off value between these two groups could be determined (▶ **Fig. 4**).

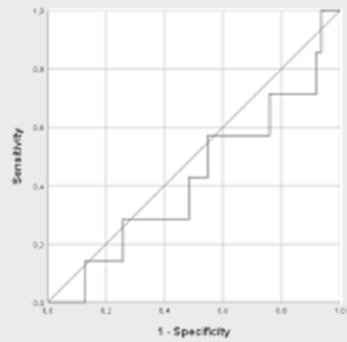
A comparison of the individual course of serum cortisol levels showed that the presence of a peak of cortisol in the early postoperative course was associated with later recurrence (▶ **Table 1**, ▶ **Fig. 1**). Thus, only 22.5 % of patients with long-term remission showed a peak, whereas this was detectable in 87.5 % of patients with later recurrence (p = 0.001). The time to peak did not show a significant difference between patients with or without recurrence. There was also a correlation between the immediate postoperative outcome and recurrence rate: patients with later recurrence after remission showed a delayed decrease of 37.5 %, whereas those with persisting long-term remission showed a delayed decrease of only 6.9 %. However, patients with later recurrence showed a significantly longer duration of follow-up than patients with long-term remission (p = 0.005).

Quality of cortisol level to predict long-term outcome

The ROC curves from 8 pm on the day of surgery to 8 am on POM1 all showed an AUC greater than 0.8, which was significant (p < 0.05). The largest AUC value was obtained on POD1 at 4 am.

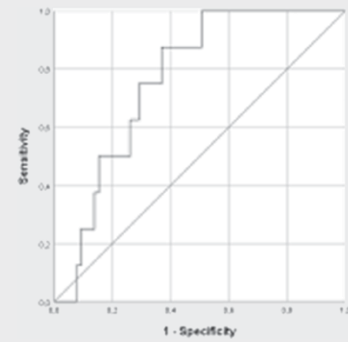
The sensitivity reached a value of 1 at all measuring times, suggesting that all patients with a following recurrence had a cortisol value above the cut-off value. Similarly, an NPV of 1 could be determined at all measuring times from 8 pm onward. Moreover, as soon as the cortisol value was below this cut-off value, long-term remission was observed in these patients. However, because several patients with long-term remission also had a cortisol value above the cut-off value, the specificity only reached values between 0.635 (8 am) and 0.742 (4 am). The PPV varied between 0.258 and 0.333.

The most informative cortisol value was measured on POD1 at 4 am. On the one hand, all patients with a recurrence following intraoperative



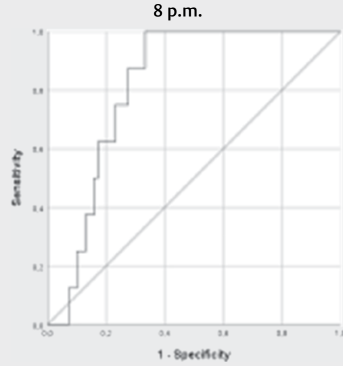
Cut-off	113.45	AUC	0.424 (p = 0.512)
Sensitivity	1	PPV	0.108
Specificity	0.065	NPV	0.8

4 p.m.



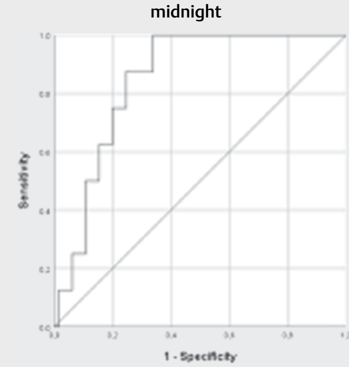
Cut-off	172.05	AUC	0.763 (p = 0.064)
Sensitivity	0.875	PPV	0.226
Specificity	0.631	NPV	0.976

8 p.m.



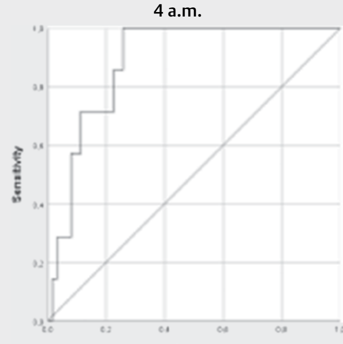
Cut-off	119.6	AUC	0.815 (p = 0.004)
Sensitivity	1	PPV	0.258
Specificity	0.667	NPV	1

midnight



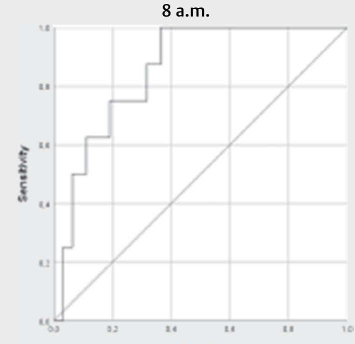
Cut-off	54.8	AUC	0.846 (p = 0.001)
Sensitivity	1	PPV	0.267
Specificity	0.662	NPV	1

4 a.m.



Cut-off	51.85	AUC	0.885 (p = 0.001)
Sensitivity	1	PPV	0.304
Specificity	0.742	NPV	1

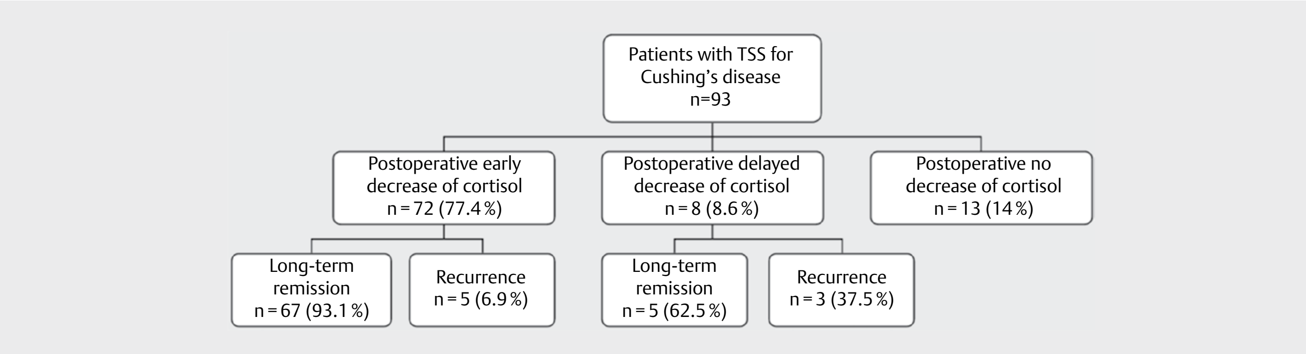
8 a.m.



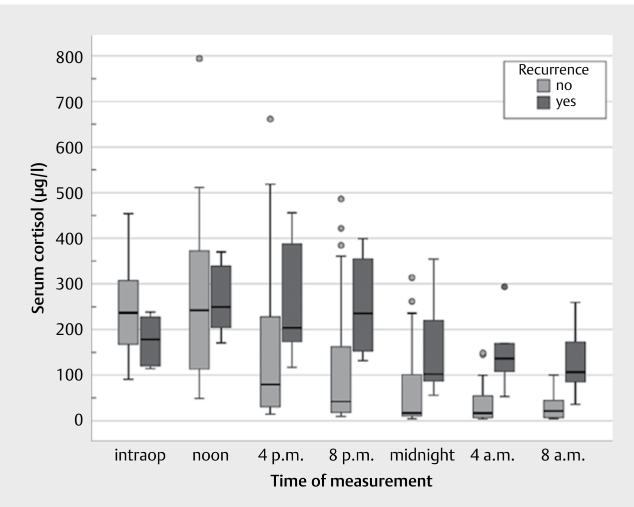
Cut-off	35.6	AUC	0.835 (p = 0.001)
Sensitivity	1	PPV	0.258
Specificity	0.635	NPV	1

▶ **Fig. 2** Receiver operating characteristic (ROC) curves based on the outcome “recurrence.”; (Cut-off: cortisol value in μg/L, NPV: negative predictive value, PPV: positive predictive value, AUC: area under the curve).

remission had a cortisol value above 51.85 μg/L (specificity = 1); on the other hand, 74.2 % of patients with a long-term remission had a cortisol value measured below this cut-off value (specificity = 0.742). Moreover, as soon as a value below 51.85 μg/L was measured, no following recurrence occurred in 100 % of these patients (NPV = 1). However, only less than one-third of the patients with recurrence could be correctly predicted based on this cut-off value (PPV = 0.304). Thus, out of 23 patients with a serum cortisol value above the cut-off value, 16 showed long-term remission, and seven developed a recurrence later on.



▶ **Fig. 3** Early and long-term outcomes in patients with Cushing's disease after transsphenoidal surgery (TSS).



▶ **Fig. 4** Box plots of intraoperative and postoperative serum cortisol levels in patients with long-term remission and recurrence (intraop: intraoperative).

Predictors of recurrence

In the multivariate analysis, the significant parameters identified by univariate analysis (▶ **Table 2**) were tested in a joint model after other parameters were excluded from univariate analysis for not showing any improvement in the regression model. The variable "C1_04" was not analyzed further in case of a non-significant regression coefficient (B) (p = 0.07). Overall, only the occurrence of a peak in serum cortisol was found to be significant (▶ **Table 3**). In the presence of a peak in serum cortisol during the postoperative course, the chance of recurrence was 20 times higher compared with patients who did not have a peak (95 % CI: 2.036–196.499).

Discussion

Patient cohort

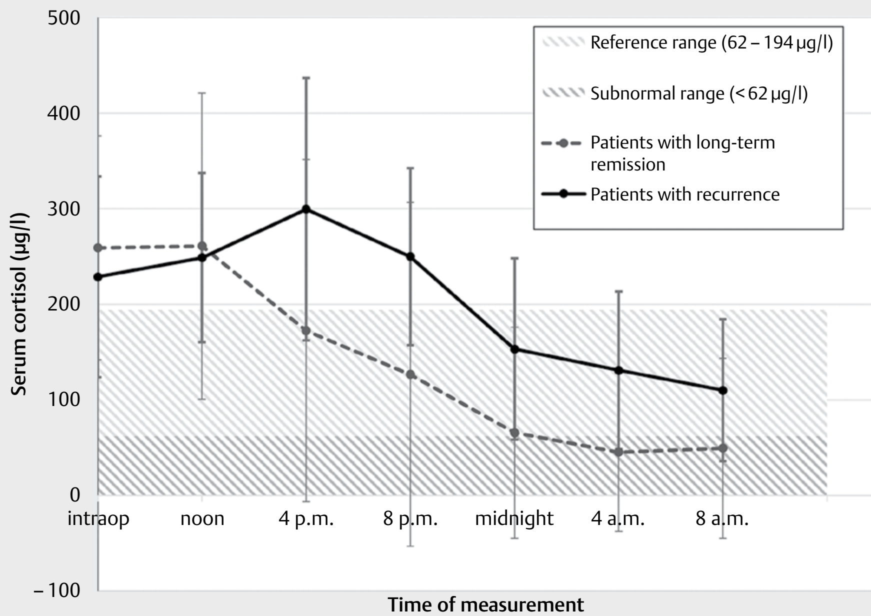
This study included primary treatment of Cushing's disease (including early re-operations within four weeks, n = 72) and cases with previous operations done elsewhere (n = 21). Several other studies partially preselected at this point and included only patients who had undergone primary treatment of Cushing's disease [12–15], whereas other studies used data from patients with primary and secondary operations [16–18]. The outcome of secondary surgery in patients with Cushing's disease is reported to be worse compared to primary surgery [19–22]. Reasons for the poorer outcome after re-operation may be manifold: on the one hand, primary surgery might have segmented the adenoma and possibly spread it within the surgical site; on the other hand, the formation of scar tissue may make orientation and access difficult for the surgeon [9, 23, 24]. Moreover, ectopic ACTH-secreting adenomas may have been overlooked [25]. Thus, to compare other studies with the endpoint of outcome after TSS, it should also be mentioned whether only primary and/or re-operations were included.

Perioperative management

In the surgeries studied in our cohort, no glucocorticoids were routinely administered perioperatively unless secondary adrenal insufficiency was diagnosed. Contrary to this approach, there are several therapeutic protocols that administer various forms of glucocorticoids intraoperatively and postoperatively at different times. The reason for glucocorticoid administration is to prevent hypocortisolemia symptoms and its maximum variant in the form of Addisonian crisis. However, to determine postoperative serum cortisol levels and early postoperative outcomes in patients with Cushing`s disease, interruption of glucocorticoid administration must be attempted [8, 13, 14, 16, 19, 21, 25, 32]. However, the extent to which perioperative glucocorticoids affect the usability of early postoperative cortisol to determine the early outcomes after TSS is not clear [26, 27]. Perioperative management should be considered when comparing studies on the outcome of TSS in Cushing's disease. In our cohort of adult patients without any perioperative glucocorticoid administration, we did not observe any Addisonian crisis in the early postoperative course.

Interpretation of postoperative result

There are no internationally accepted criteria for detection of early remission after surgical therapy for Cushing's disease, and therefore there is no consensus on the tests or laboratory examinations performed postoperatively nor their timing. Different studies use



▶ **Fig. 5** Mean serum cortisol levels of patients with long-term remission and recurrence ± Standard Deviation (intraop: intraoperative).

different definitions regarding the remission of Cushing's disease [5, 7, 12, 16, 25, 28–31]. However, setting a cut-off value on POM1 after surgery as this study attempted to achieve for the interpretation of an "early" compared to "delayed remission" seems to be rather early compared to other studies [13, 33–35].

Operating results

In three large meta-analyses [36–38], postoperative remission rates ranged from 76 % to 78 % (range: 25–100 %). The postoperative remission rate of 86 % determined in our series (▶ **Fig. 3**) is significantly higher than the average literature results. The recurrence rates in the studies mentioned above were reported to be 15.2 %, 13.2 %, and10 %. Therefore, the recurrence rate of 10 % determined in this study corresponds to the lower spectrum of the international range. If we look at primary surgeries (including early re-operations) only, the postoperative results are even better (postoperative remission: 90.3 %, recurrence rate: 10.8 %, long-term remission rate: 80.6 %).

Predictors of outcome

Several studies have shown that the immediate postoperative remission rate of patients with microadenomas was significantly higher than that of patients with macroadenomas [5, 7, 13, 15, 20, 38–40]. Re-operations in other studies were also significantly more often followed by the persistence of Cushing's disease compared to primary surgeries [7, 40–43]. A worse outcome in the presence of an invasive adenoma, i. e., a higher rate of both postoperative persistence and later recurrence, has been demonstrated by some other studies as well [7, 20, 44, 46]. However, the different definitions of remission, persistence, and recurrence, on the one hand, and the different statistical methods, on the other hand, should be considered [36].

The positive association between the presence of a postoperative serum cortisol decline and long-term remission has also been reported earlier [8, 16, 45]. In our cohort, significant differences ($p = 0.001$-.0.016) between patients with recurrence and long-term remission were seen at all times of measurement, starting from 4 pm. Of particular note is that postoperative serum cortisol levels were measured at shorter time intervals (four hours) compared to most other studies, whereby the risk of symptomatic hypocortisolism could be minimized. Apart from the different postoperative management, some other studies have already shown that postoperatively decreased serum cortisol levels are associated with a better outcome [10–13, 15, 20, 24, 25, 44], which could be confirmed here as well (▶ **Table 1**). In addition to cortisol, which must be determined in the postoperative course to detect adrenal insufficiency, ACTH levels can also be determined postoperatively; ACTH alone offers no advantage compared to cortisol in terms of operative success [47]. However, some studies suggest that elevated ACTH levels (> 20 ng/L) in the presence of hypocortisolism after TSS for Cushing's disease indicate an increased risk of recurrence [29, 48]. We could not confirm these findings in our cohort: although the ACTH values on POM1 were higher when a recurrence occurred later, this difference was statistically not significant (▶ **Table 1**).

The mean duration of follow-up in this series was 48 months, which is rather short. With the low recurrence rate of 10 % compared to other studies [36–38], the significantly longer duration of follow-up of patients with recurrence (▶ **Table 1**) should be considered. Several factors may lead to the discontinuation of follow-up. As seen here, the longer the follow-up, the greater the recurrence rate. Hypothetically, a certain number of patients classified as being in "long-term remission" would have experienced a recur-

▶ **Table 1** Comparison of different parameters regarding the long-term result.

	Long-term remission n = 72	**Recurrence n = 8**	**p-value**
Age (years)	41.53 ± 12.411 (13–66)	42.13 ± 11.37 (23–55)	0.904
Female	52 (72.2 %)	6 (75 %)	1.000
Diameter (mm)	6.587 ± 6.016 (1.5–36.0)	12.286 ± 10.531 (3.0–26.0)	0.264
Macroadenoma	9 (14.3 %)	3 (42.9 %)	0.092
Reoperation	14 (19.4 %)	1 (12.5 %)	1.000
C0_intra (µg/L)	259.082 ± 116.978 (51.9–608.8)	228.743 ± 104.883 (114.4–403)	0.512
C0_12 (µg/L)	260.918 ± 160.123 (49–793.9)	248.683 ± 88.52 (158.4–370.1)	0.947
C0_16 (µg/L)	172.477 ± 178.945 (14.3–831.9)	299.413 ± 137.012 (117.4–482.4)	**0.016**
C0_20 (µg/L)	126.739 ± 179.779 (7.5–1080)	249.900 ± 92.56 (132.0–399.2)	**0.004**
C1_00 (µg/L)	65.763 ± 110.318 (4.4–754)	153.263 ± 94.737 (56.0–354.6)	**0.001**
C1_04 (µg/l)	45.344 ± 82.711 (3.0–599.9)	130.886 ± 82.473 (52.9–293.6)	**0.001**
C1_08 (µg/l) POM1	49.635 ± 93.953 (4.0–582.2)	110.1 ± 74.247 (35.8–259.3)	**0.001**
ACTH at POM1 (ng/l)	68.864 ± 41.948 (4.1–232.6)	93.2 ± 10.1823 (86–100.4)	0.187
Peak of serum cortisol	16 (22.2 %)	7 (87.5 %)	**0.001**
Peak height	59.256 ± 85.164 (4.1–361.1)	47.157 ± 37.044 (9.2–118.1)	0.974
Time to peak (h)	24.19 ± 13.408 (9–53)	18.43 ± 11.516 (5–41)	0.175
Invasiveness yes	19 (26.4 %)	4 (50 %)	0.077
Postoperatively early decrease delayed decrease	67 (93.1 %) 5 (6.9 %)	5 (62.5 %) 3 (37.5 %)	**0.03**
Follow-up (months)	43.81 ± 28.36 (12–120)	84.63 ± 39.91 (26–129)	**0.005**
Histology			
negative	11 (16.9 %)	/	0.309
sparsely granulated	20 (30.8 %)	5 (62.5 %)	
densely granulated	33 (50.8 %)	3 (37.5 %)	
Crooke c.a.	1 (1.5 %)	/	

C0_intra: highest intraoperative cortisol value. Cortisol values are expressed in µg/L and given in 4 h intervals. Peak of serum cortisol: individual peak of serum cortisol in the early postoperative course. Peak height: Difference between the cortisol value of a peak and its lowest previous value. In case of more than one peak in the postoperative course of serum cortisol, the first peak was used. FU: duration of follow-up. Crooke c.a.: Crooke cell adenoma. Values are given as mean ± standard deviation (minimum-maximum) or as absolute and relative numbers (%).

▶ **Table 2** Significant parameters identified by univariate binary logistic regression analysis.

Variable	**Manifestation**	**B**	**Significance**	**ExpB**	**95 % CI of ExpB**	
C1_4 am	/	0.007	0.07	1.007	0.999	1.014
Peak of serum cortisols	no			Reference group		
	yes		**0.004**	24.062	2.753	210.323
Postoperative outcome	early decrease			Reference group		
	delayed decrease	2.084	**0.016**	8.04	1.476	43.809

B: regression coefficient; ExpB: Odds Ratio; 95 % CI: 95 % confidence interval; C1_4 am: Cortisol level at 4 am on the first postoperative day.

▶ **Table 3** Multivariate binary logistic regression analysis. The significant parameters identified by univariate analysis were tested in a joint model.

Variable	**B**	**Significance**	**ExpB**	**95 % CI von ExpB**	
Peak of serum cortisol	2.996	**0.01**	20	2.036	196.499
Postoperative outcome	0.501	0.592	1.650	0.264	10.313

B: Regression coefficient; ExpB: Odds Ratio; 95 % CI: 95 % confidence interval.

rence if they had been followed longer. However, most relapses of Cushing`s disease occur within the first two postoperative years [10], as is also seen in our cohort.

Some studies took a deeper dive into postoperative cortisol dynamics, measured cortisol levels at different times, and assessed whether they allow conclusions regarding the early postoperative outcome or long-term outcome. In a study by Hameed et al. [23], a postoperative serum cortisol level of < 20 µg/L within 48 h after surgery showed a PPV of 100 % for long-term remission. In a study of 257 patients, Ironside et al. [45] reported that 8.7 % of patients with postoperative serum cortisol of < 50 µg/L (within 10 days) relapsed, whereas this was the case in only 5.9 % of patients with serum cortisol of < 20 µg/L. In contrast, Lindsay et al. [16] found no significant difference in recurrence rates between patients with a serum cortisol level < 20 µg/L and < 50 µg/L (9.4 vs. 10.4 %). In a meta-analysis of 5664 patients by Stroud et al. [43], patients with a postoperative cortisol nadir of < 20 µg/L showed both an increased rate of postoperative remission (95 vs. 46 %) and a lower rate of following recurrence (10 vs. 37 %). However, recurrence rates of 15 % in patients with a postoperative serum cortisol level of < 18 µg/L in a study on 131 patients [46] and 11.5 % in patients with undetectable serum cortisol in a study on 97 patients [26] were also seen. In the study presented here, no patient with a cortisol value below 51.85 µg/L at 4 am and 35.6 µg/L at 8 am on POD1 later on showed a recurrence during follow-up.

Some studies have determined the sensitivities and specificities of postoperative serum cortisol levels for achieving recurrence or long-term remission: Ironside et al. [45] reported that a cut-off value of serum cortisol of 33 µg/L at 6 am on POD1 provided a sensitivity of 100 %, specificity of 59 %, and NPV of 100 % for predicting long-term remission. In addition, a cut-off value of 185 µg/L on POD3 at 6 am was calculated, which achieved a sensitivity of 14 %, specificity of 98.6 %, and PPV of 92 % for predicting recurrence. Another study calculated a cut-off value of 53.5 µg/L on POD2, which achieved a PPV of 97 %, and an NPV of 73 % for reaching remission at six months [41]. Compared to these studies, the present study showed similar or even better values for sensitivity, specificity, or NPV for the earliest time of measurement (4 am on POD1) reported so far. Furthermore, other studies, like ours, also failed to identify a clear cut-off value to accurately predict recurrence or remission [16, 23, 25]. One should be critical about the calculation of the cut-off value using the Youden index, in which sensitivity and specificity have equal importance. Although all the patients in our study with a following recurrence had serum cortisol above the cut-off value at 4 am on POD1 (sensitivity = 1), this was also true for 16 of 62 patients with long-term remission (specificity = 0.742).

In addition to the absolute values, the individual course of the postoperative serum cortisol was determined and evaluated in this study (▶ **Table 1**, ▶ **Fig. 1**). Such a differentiated analysis of postoperative cortisol dynamics has not been reported before. The presence of a peak in the postoperative course of serum cortisol may be caused by small tumor remnants, which initially still secrete ACTH and whose function decreases within a short period due to the damage induced by the operation but thereafter recover and cause the recurrence seen later on.

In our data, not only the event of a peak of serum cortisol in the postoperative course was statistically highly different between patients with and without later recurrence (87.5 vs. 22.5 %, p = 0.001), but also binary logistic regression showed that *only* a peak of serum cortisol in the postoperative course significantly contributed to explaining the probability of recurrence in our data (ExpB = 20.95 %; CI = 2.036–196.499; p = 0.01). Further studies are needed to generate more reliable data on the significance of very early postoperative serum cortisol progression.

Limitations

The serum cortisol levels were collected prospectively, and the data sets were evaluated retrospectively. In the face of minimal loss to follow-up, the patient cohort of 93 consecutive individuals seems to be rather large, taking the rare instance of Cushing's disease into account. The significantly shorter duration of follow-up of patients with long-term remission compared to patients with recurrence limits the value of this study. However, due to the limited number of patients in this monocenter study, particularly the relatively small number of patients with recurrence (n = 8) and the fact that only the presence of a peak, but not its height, has an influence on the outcome, one cannot exclude them as random physiological cortisol fluctuations. Our results should be verified by further studies.

A total of nine surgeries started and ended late; therefore, the time interval between cortisol measurements and the end of surgery was not consistent. Thus, while the majority of the surgeries were finished at around 11 am, the delayed surgeries could only be finished between 12 and 3 pm. On the one hand, some values for 12 am are missing; on the other hand, the time intervals to the end of surgery partly differ by several hours. However, since the number of cases (n = 9) and the temporal deviation (maximum of 4 hours) are relatively small and a clear difference in the cortisol values only became apparent at later time points, the influence of the delayed operations should not be too great.

Patients with recurrence may differ with respect to pathology and thereby secretory pattern and varying kinetics of post-surgical cortisol. Although there was no significant difference in histology between these two groups, group differences may not be detected by histology but only by molecular analysis. Combining primary and secondary surgery in this study presents a potential bias in the analysis of predictive factors.

Conclusions

Cortisol levels at 8 am are easy to obtain. A value of 35.6 µg/L showed an NPV of 1 and therefore identified all patients with ongoing remission. Furthermore, patients with an upward peak of serum cortisol in the very early postoperative course show an increased recurrence rate later. This may allow an assessment of the long-term prognosis in individual cases as early as one day after surgery.

Acknowledgments

This work contains essential parts of the thesis of M. Meier.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflict of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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